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(54) Title: LIGNANS, A PROCESS FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

(57) Abstract

The present invention provides a process for the production of lignan derivatives, which comprises the step of subjecting benzyl substituted succinyl diesters to a Stobbe condensation using lithium methanolate as base in order to produce dibenzyl substituted half esters of succinic acid, which may subsequently be converted into the lignans. Additionally, novel lignans are provided by the invention, as well as pharmaceutical compositions containing these compounds. Furthermpre the use of lignans in the manufacture of medicaments effective as SHBG inhibiting agents, anti-tumour agents and agents against prostate cancer is described.

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Lignans, a Process for their Production and Pharmaceutical Compositions and uses thereof

The present invention relates to a process for the production of lignans as well as novel lignans which may be produced by this process. It furthermore concerns pharmaceutical compositions containing those lignans which find use as human sex hormone binding inhibitors, anti-tumour agents and agents against prostate cancer.

It is known that lignans can be separated from plant extracts, such as from Coniferae (e.g. Spruce), Magnolia (e.g. Magnolia Fargesii), and Nettle root. It is also known that such lignans may display a wide variety of physiological effects in mammals. Examples of this activity include fertility enhancement when acting as blood platelet activating factors, (O' Neill, PCT patent application no. WO/90 13299), spasmolytic activity when used as anti-hiccough agents, (Matsuura *et al*, *Phytochem.*, vol. 24, p. 626, 1985), and interference with Human Sex Hormone-Binding Globulin (SHBG) (Ganßer and Spiteller, *Z. Naturforsch.* 50c, p. 98, 1995).

In regard to the development of useful pharmaceuticals comprising lignans, it was naturally necessary to have the active compounds available in considerable quantities, and the problem of realising a synthetic route to lignans thus arose. Morimoto *et al* developed an asymmetric synthesis to several lignans using chiral bisphosphine ligands and Rhodium

(I) catalysed asymmetric hydrogenation. In this way (-)-matairesinol and (-)-anhydrosecoisolariciresinol were produced, (*Heterocycles*, vol. 33, p. 435, 1992), however such methods are not industrially practical in terms of cost, time and yield. An oxidative coupling reaction has been used to produce the lignans enterolactone and wikstromol (J. Belletire *et al, Tet. Lett.*, vol. 27, p. 127, 1986 and *J. Org. Chem.*, vol. 53, p. 4724, 1988). This method has been applied in several Japanese patent applications for producing lignans of the type isolable from Nettle root (JP-A-88 186853, JP-A-88 250002, JP-A-88 53550). These lignans are indicated to be useful in immuno-suppressant, cardiotonic and anti-tumour compositions respectively. However, these processes necessitate the use of protection groups on the phenol residues, and must be carried out under strict anhydrous conditions in an inert atmosphere, considerably limiting the available yield of pure product. Further methods of production using a Stobbe condensation have been attempted (Matsuura *et al*, *Phytochem.* vol. 24, p. 626, 1985, Brown, *et al*, *Heterocycles*, vol. 26, p. 1169, 1987, and Bambagotti-Alberti, *et al*, *Heterocycles*, vol. 27, p. 2185, 1988) using sodium alcoholate, lithium alcoholate and sodium hydride as bases, respectively. However, condensation with a second aromatic group was achieved through laborious methods involving the use of protection groups on the phenol residues.

Thus, before the achievement of the present invention the problems still remained of determining which particular lignans (especially those isolable from Nettle root), possessed significant interference properties with SHBG, and furthermore of determining the strength of this activity, and the pharmaceutical effects of the compounds.

Additionally an economical and industrially viable process route into these compounds was required before pharmaceuticals comprising these compounds could be effectively produced.

Thus an objective of the present invention is to develop a novel synthesis of lignans, so that they may be produced more easily and on a more commercially viable scale.

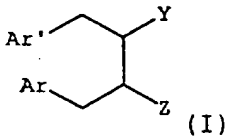
A further objective is to provide new lignans which were not previously obtainable from natural sources and could also find use as pharmaceuticals.

Furthermore, the intent was to provide pharmaceutical compositions containing the lignans, especially those which act as SHBG inhibitors. Therefore, further objectives include the determination of the activities of the lignans, and the formation of appropriate pharmaceuticals. A related further objective was to develop the use of the lignans in the treatment of particular ailments.

In attempting to solve these problems, the present inventors developed a new mode of synthesis for lignans, making use of two consecutive Stobbe condensations, using lithium alcoholate as a base. This method is particularly advantageous as it does not require the use of protection groups, nor are such rigorous anhydrous, inert-atmosphere conditions needed. Thus, the process affords a quicker, more simple route into the target compounds, which can be produced in improved yield and purity than has thus far been disclosed in the prior art. Furthermore non-symmetric lignans are also easily produced.

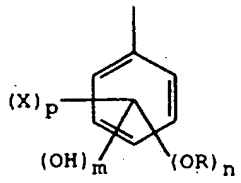
Through the use of this process, new lignans, not previously isolated from natural sources were produced, which were determined to be active as SHBG inhibitors. Furthermore, pharmaceutical compositions were developed comprising these compounds, and it was determined that the lignans have a beneficial pharmaceutical effect when used against tumours and prostate cancer.

Therefore, according to the present invention a process for the production of compounds of formula (I) is provided:



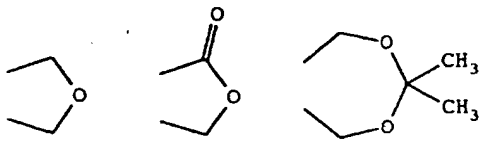
(I)

wherein Ar and Ar' may be the same or different and are represented by groups of the following formula:

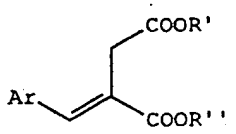


wherein X is a halogen atom, a C_1 to C_6 alkyl group, an amino group, a nitro group, an acyl group (CH_3COO-), a carboxylic acid group or a C_1 to C_6 alkyl ester of a carboxylic acid, a phenyl group, or a phenyl group substituted with any of the above groups; R is a C_1 to C_6 stright chain or branched alkyl group; and n, m and p are integers of 0 to 5, provided that the sum of n, m and p does not exceed 5; and Y and Z may be the same or different and represent COOH, COOR', CH_2OH, or

CH_2OR' groups or taken together may represent any groups of the following formulae:

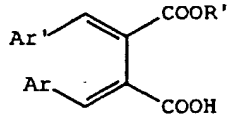


comprising step (1), of reacting a compound of formula (Ia):



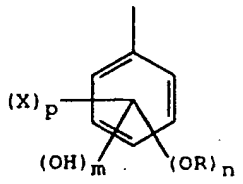
(Ia)

with a lithium/R'OH, or a lithium/R''OH mixture in the presence of Ar'-CHO, wherein R' and R'' may be the same or different and are C_1 to C_6 straight chain or branched alkyl groups, or phenyl groups to form an intermediate compound (Ib):



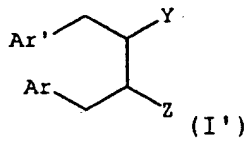
(Ib)

It should be noted that when groups such as



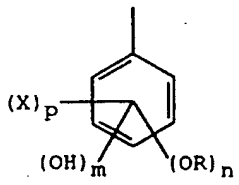
are mentioned it is intended to indicate that they are bound to the general formula by the hanging bond(s) indicated.

Furthermore, lignan compounds of the following formula (I') are provided in the invention:

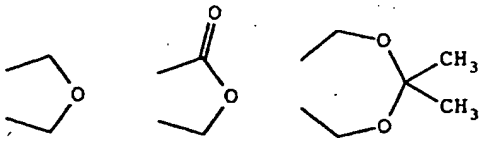


(I')

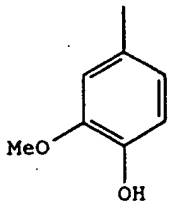
wherein Ar and Ar' may be the same or different and are represented by groups of the following formula:



wherein X is a halogen atom, a C_1 to C_6 alkyl group, an amino group, a nitro group, an acyl group (CH_3COO-), a carboxylic acid group or a C_1 to C_6 alkyl ester of a carboxylic acid, a phenyl group, or a phenyl group substituted with any of the above groups; R is a C_1 to C_6 straight chain or branched alkyl group; and n, m and p are integers of 0 to 5, provided that the sum of n, m and p does not exceed 5; and Y and Z may be the same or different and represent COOH, COOR', CH_2OH, or CH_2OR' groups or taken together may represent any groups of the following formulae:

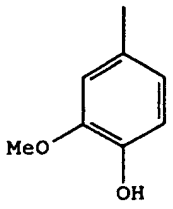


wherein, compounds having p = 0, (m + n) = 3 or less and R = Me are not claimed, except where Ar' is a group of formula:

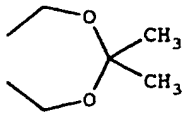


and either:

Ar is a group of the following formula:

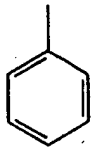


and Y and Z are both COOR' groups, or together form group of formula



or:

Ar is a group of formula:

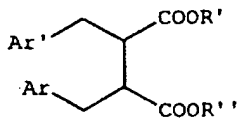


and Y and Z are both COOR' groups, or both a CH_2OH group, or together form a group of formula:

wherein when Y and Z are COOR', the groups R' may be the same or different and are C_1 to C_6 straight chain or branched alkyl groups or phenyl groups.

Additionally, the invention provides the use of compounds of formula (I) in the manufacture of medicaments effective as human sex hormone-binding globuline inhibitors, anti-tumour agents and agents against prostate cancer. Furthermore pharmaceutical compositions comprising compounds (I') are provided.

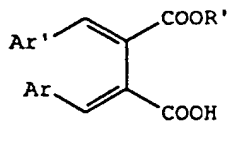
A preferred process of the present invention, is one in which compounds of the formula (I) are produced in which Y and Z are groups of formula COOR' and COOR'', i.e. compounds of formula (II):



(II)

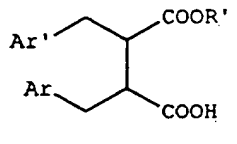
in which Ar, Ar', R' and R'' have the same meanings as described above. A preferred route from compounds (Ib) into compounds (II) comprises the following steps:

(2) Reducing compounds of formula (Ib),



(Ib)

to produce compounds of formula (Ic);

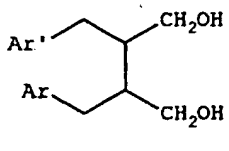


(Ic)

(3) Subjecting compounds (Ic) to esterification, to produce compounds of formula (II).

The conditions and reagents for effecting the reduction and esterification steps are not particularly limited, however, for the step of reduction, hydrogen on a palladium/carbon catalyst is particularly preferred, and for the esterification step the use of R''OH in the presence of sulphuric acid is preferable. The reduction and esterification steps can be carried out in the reverse order if desired.

A further preferred process of the present invention, is one in which compounds of the formula (I) are produced in which both Y and Z are CH_2OH groups, i.e. compounds of formula (III):

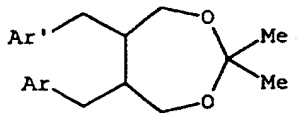


(III)

in which Ar and Ar' have the same meanings as described above. A preferred route from compounds (Ib) into compounds (III) comprises steps (2) and (3) as described above and the additional step:

(4) reducing compounds (II) to form compounds (III).

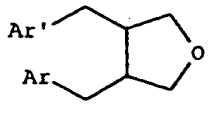
The conditions and reagents for effecting this reduction step are not particularly limited, however, it is most preferably carried out using $LiAlH_4$. Compounds (III) can additionally be transformed into compounds (III'), if so required, by reaction with acetone in the presence of acid:



(III')

Another preferred process of the present invention, is one in which compounds of the formula (I) are produced in which Y and Z taken together represent a group of formula:

i.e., compounds of formula (IV):



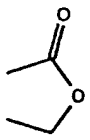
(IV)

in which Ar and Ar' have the same meanings as described above. A preferred route from compounds (Ib) into compounds (IV) comprises steps (2), (3) and (4), as described above and the additional step:

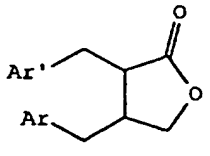
(5) Subjecting compounds of formula (III) to a cyclisation reaction, to produce compounds of formula (IV).

The conditions and reagents for effecting this reduction step are not particularly limited, however, it is most preferably carried out using $HClO_4$. Other acids and also Al_2O_3 can be used if desired.

A still further preferred process of the present invention, is one in which compounds of the formula (I) are produced, in which Y and Z taken together represent a group of formula:



i.e., compounds of formula (V):



(V)

in which Ar and Ar' have the same meanings as described above. A preferred route from compounds (Ib) into compounds (V) comprises step (2), as described above, to form compounds (Ic) and the additional step:

(6) Subjecting compounds of formula (Ic) to a cyclisation reaction to form compounds of formula (V);

The conditions and reagents for effecting this cyclisation step are not particularly limited, however, it is most preferably carried out using $LiAlH_4$, followed by the application of hydrochloric acid.

When $p > 0$, the preferred substituents for group X are a halogen atom (fluorine, chlorine, bromine or iodine), a C_1 to C_6 alkyl group (methyl, ethyl, propyl, butyl, pentyl or hexyl) or an acyl group (CH_3COO-).

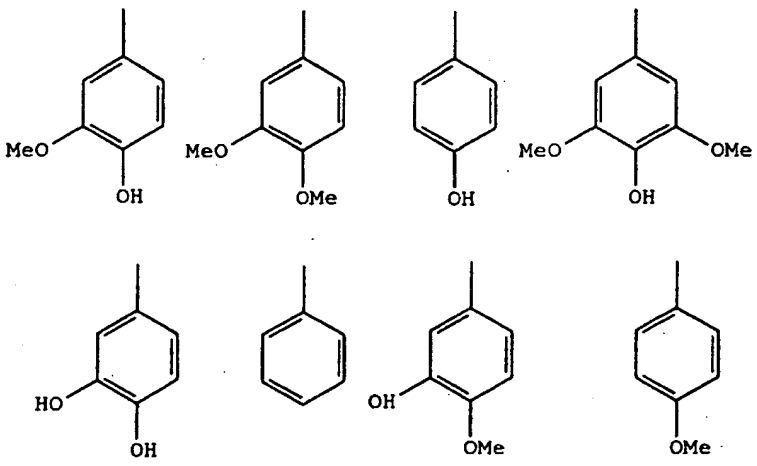
The process of the invention can be practised well for compounds in which $p > 4$, however, compounds in which $p = 4$ or less are preferred. Of increasing preference are those compounds in which $p = 3$, $p = 2$, and $p = 1$ and compounds wherein $p = 0$ are most preferred. Non-symmetric compounds ($Ar \neq Ar'$) can be easily produced by the process of the invention, however it is particularly preferred for symmetric compounds.

The inventors have determined that lignans having at least one hydroxyl group and/or at least one methoxy group on the aromatic residues are particularly effective as pharmaceuticals, thus processes producing compounds in which $m \geq 1$ and/or $n \geq 1$ are especially preferred. Of increasing

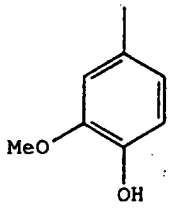
preference are those processes producing compounds wherein m = 4, m = 3, m = 0 and m = 2 and those wherein n = 4, n = 3, n = 0 and n = 2. Processes producing compounds in which n = m = 1 or (m + n) = 2 are the most preferred. The substituents RO- and HO- are preferably either in the 4- or the 3-positions on the Ar groups.

In regard to processes producing those compounds containing R, R' and R'' groups, methyl, ethyl, propyl, butyl, pentyl, hexyl and phenyl groups are specifically preferred, and of these, methyl groups are the most preferred. These groups may be chosen independently of each other, but it is preferred if R' and R'' are the same. Most preferred are processes producing compounds wherein R = R' = R'' = methyl.

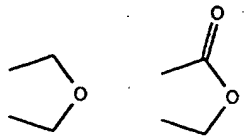
Particular specific groups which are preferred as Ar, or Ar' are:



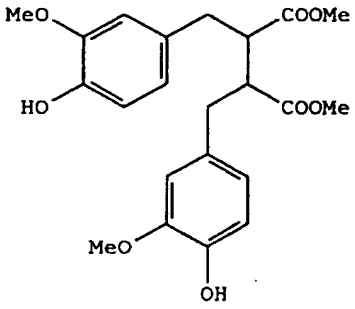
Most preferred is the group:



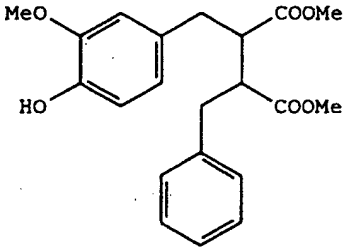
Particular preferred groups for Y and Z are the following:



with the former being most preferred. The most preferable processes are those which produce the following compounds:



(IIa)



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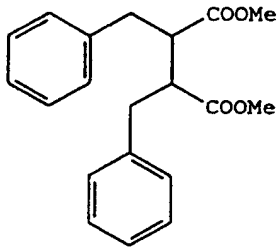
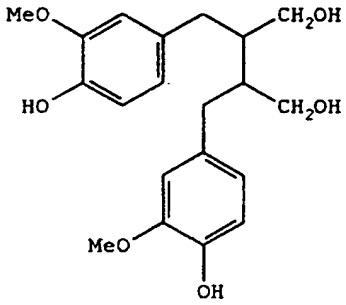
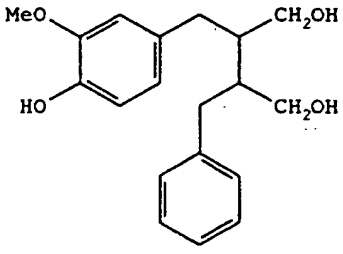


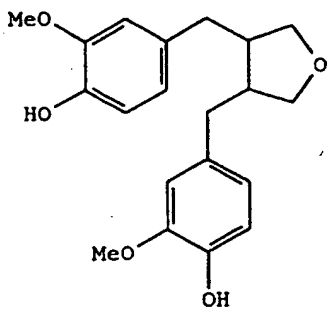
(IIc)



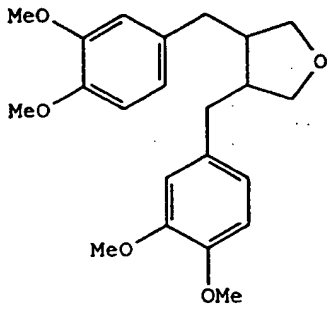
(IIIa)



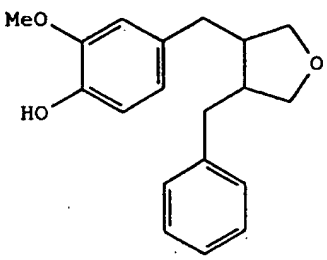
(IIIb)



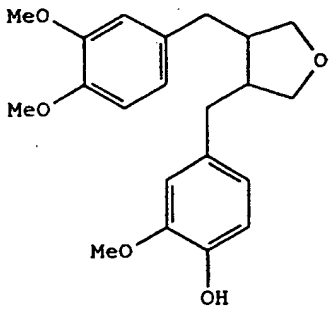
(IVa)



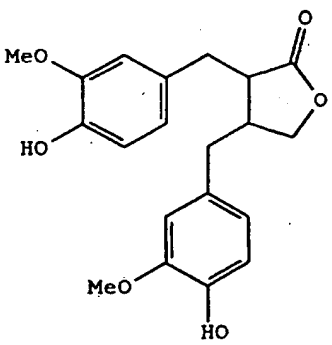
(IVb)



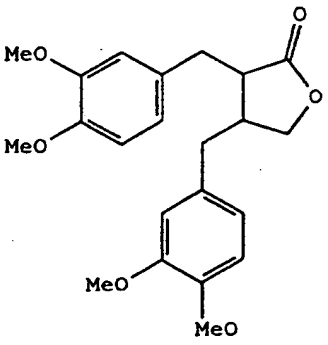
(IVc)



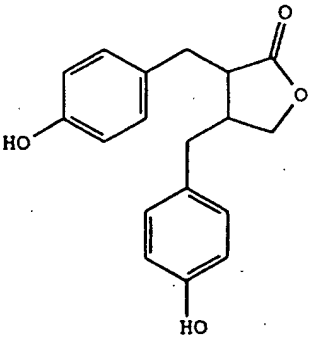
(IVd)



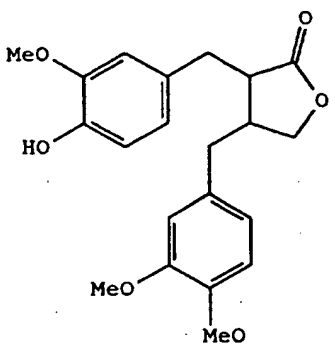
(Va)



(Vb)



(Vc)



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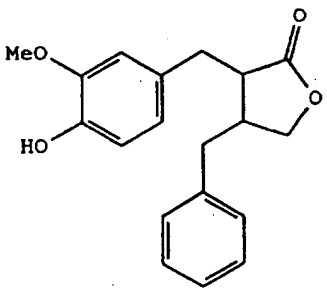
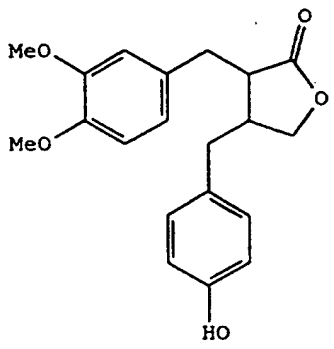
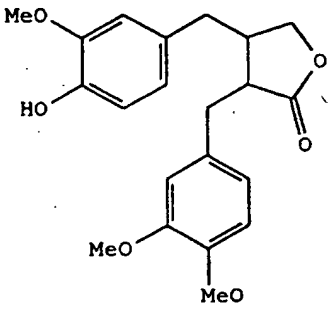


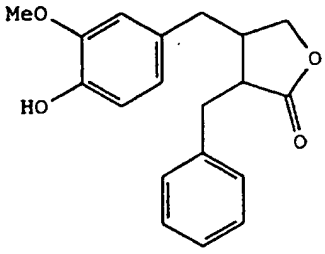
(Ve)



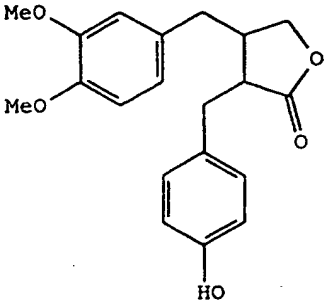
(Vf)



(Vg)

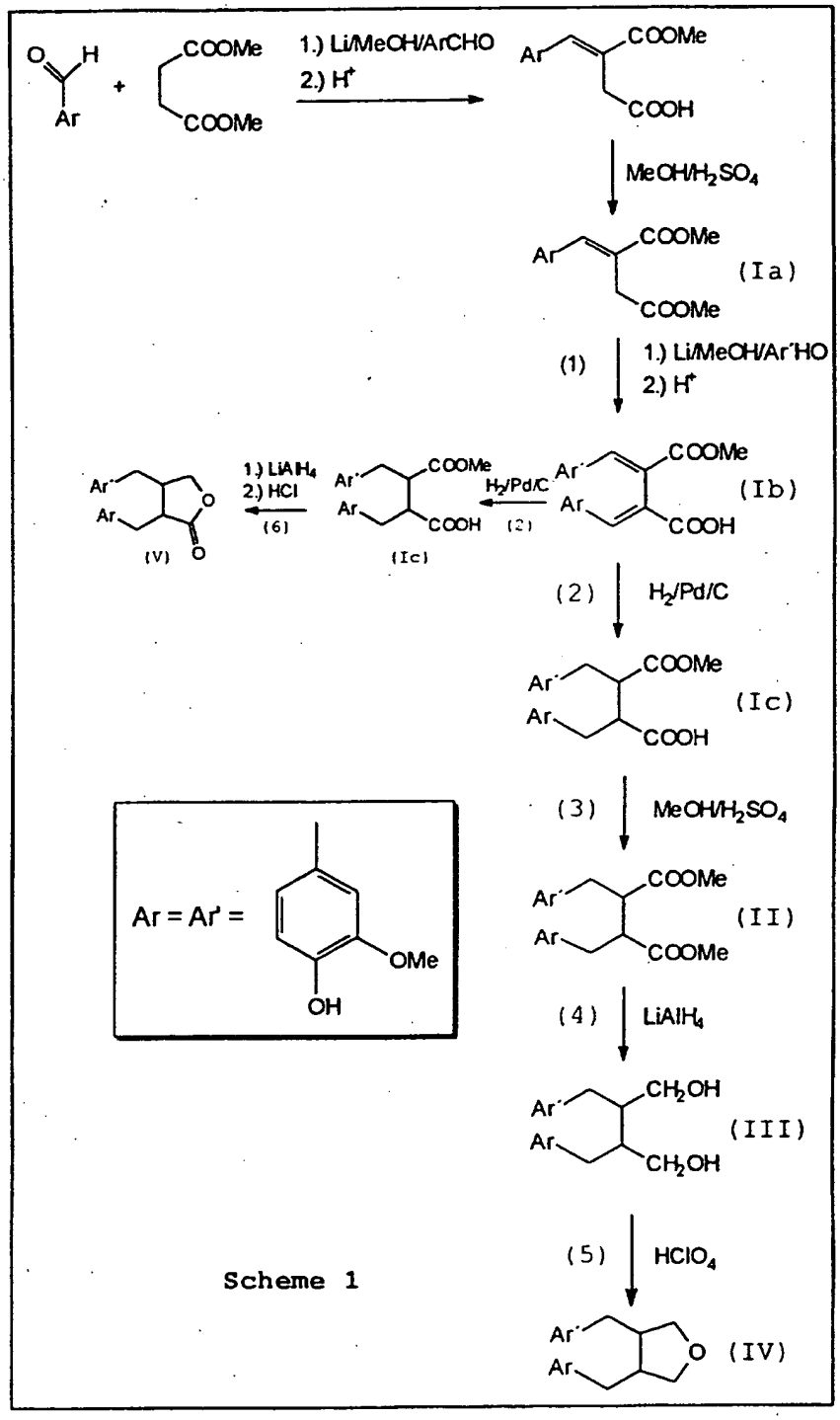


(Vh)



(Vj)

The most preferred process is one in which the compound (IVa) is produced. An overview of the most preferred route is given in Scheme 1. In this case the most preferred process of all, that producing anhydrosecoisolariciresinol is indicated, in which Ar = Ar' = 4-hydroxy-3-methoxyphenyl, along with the most preferred agents for the reactions. In addition, the related methods of production of compounds (II), (III) and (V) are depicted.


1.) Li/MeOH/ArCHO
2.) H+
COOMe
COOH
Ar
MeOH/H2SO4
(Ia)
(1)
1.) Li/MeOH/Ar'HO
2.) H+
(Ib)
H2/Pd/C
(2)
(Ic)
1.) LiAlH4
2.) HCl
(6)
(V)
(2) H2/Pd/C
(3) MeOH/H2SO4
(II)
(4) LiAlH4
CH2OH
(III)
(5) HClO4
(IV)
Ar = Ar' =
OMe
OH

Scheme 1

The most desirable processes in all cases as described above are those in which compounds (Ia) are produced via a Stobbe condensation using Ar-CHO and a diester of succinic acid, in particular using lithium methanolate as a base. However, other reagents and process steps can be utilised if required.

In the process of the present invention both the cis and the trans products are obtained, in each case in a racemic form (i.e. no enantioselectivity is displayed). Where these compounds are depicted throughout the description and claims by chemical structures in which the stereochemistry is not indicated, the structures refer to the individual cis and trans isomers, as well as mixtures thereof and also racemates if a particular isomer of the compound is chiral.

A certain strereoselectivity is observed in the process, in particular during the hydrogenation step, leading in some cases, for example, to a 2:1 excess of one isomer. With the use of Pd on active carbon, in the case of anhydrosecoisolariciresinol production, only the trans product is obtained.

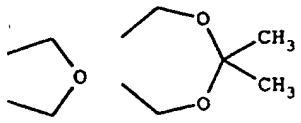
These cis and trans stereoisomers can be separated by any usual method in the art. In the case of cis isomers in which Ar = Ar' the compounds are not chiral and are therefore obtained pure after separation from the trans isomer, and when a particular isomer is chiral, it is obtained as the racemate when separated. The pure optical isomers can be obtained from the racemate by any usual separation method in the art, if desired. In the case of the most preferred compound produced according to the invention, anhydrosecoisolariciresinol, the preferred isomer is the (-)-trans isomer, although the (+)-trans and cis isomers are also desirable.

The products of the present invention are producible by the process of the present invention, and those products include those of formula (I) with the exception of a small number which are already known in the art. Thus the compounds of the present invention are defined by formula (I') as described above.

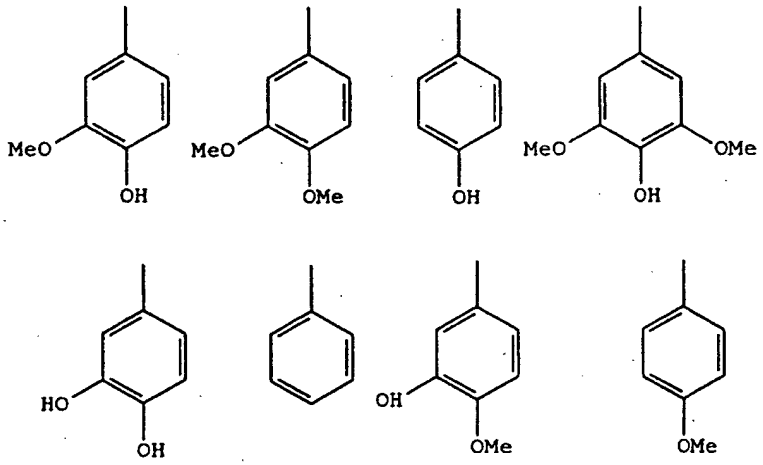
When $p > 0$, the preferred substituents for group X are a halogen atom (fluorine, chlorine, bromine or iodine), a C_1 to C_6 alkyl group (methyl, ethyl, propyl, butyl, pentyl or hexyl) or an acyl group (CH_3COO-). The invention can be practised well for compounds in which $p > 4$, however, compounds in which $p = 4$ or less are preferred. Of increasing preference are those compounds in which $p = 3$, $p = 2$, and $p = 1$ and compounds wherein $p = 0$ are most preferred. Non-symmetric compounds ($Ar \neq Ar'$) are also included, however symmetric compounds are particularly preferred.

As discussed above, the inventors have determined that lignans having at least one hydroxyl group and/or at least one methoxy group on the aromatic residues are particularly effective as pharmaceuticals, thus compounds in which $m \geq 1$ and/or $n \geq 1$ are especially preferred. Of increasing preference are those compounds wherein $m = 4$, $m = 3$, $m = 0$ and $m = 2$ and those wherein $n = 4$, $n = 3$, $n = 0$ and $n = 2$. Compounds in which $n = m = 1$ or $(n + m) = 2$ are the most preferred. The substituents RO- and HO- are preferably either in the 4- or the 3-positions on the Ar groups.

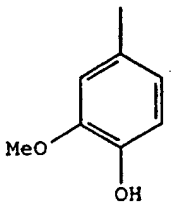
Those compounds particularly preferred are ones in which the groups Y and Z are COOR', CH_2OH or taken together are groups of the formula:



Particular specific groups which are preferred as Ar, or Ar' are:

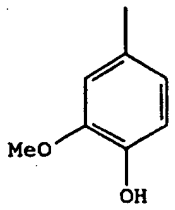


Compounds more particularly preferred are those in which Ar' in formula (I') is a group of formula:

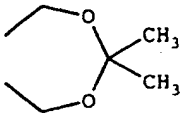


and either:

Ar is a group of the following formula:

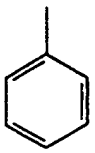


and Y and Z are both COOR' groups, or together form group of formula



or:

Ar is a group of formula:

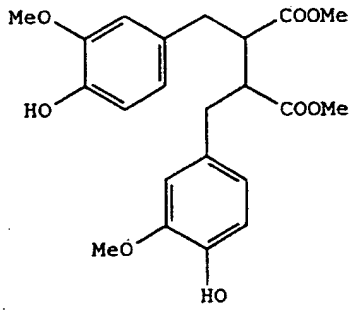


and Y and Z are both COOR' groups, or both a CH_2OH group, or together form a group of formula:

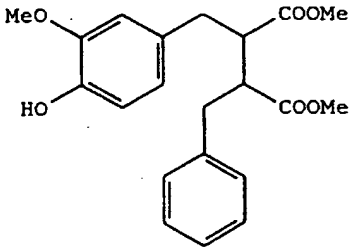
wherein when Y and Z are COOR', the groups R' may be the same or different and are C_1 to C_6 alkyl groups or phenyl groups. Compounds of this type in which Y = Z = COOR' are especially preferred.

In regard to any preferred compounds as described above containing R, R' and R'' groups, methyl, ethyl, propyl, butyl, pentyl, hexyl and phenyl groups are specifically preferred, and of these, methyl groups are the most preferred. These groups may be chosen independently of each other, but it is preferred if R' and R'' are the same. Most preferred are compounds wherein R = R' = R'' = methyl.

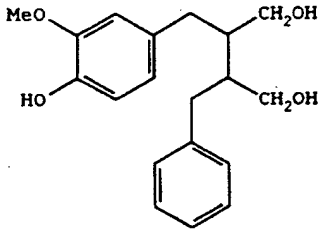
The compounds most preferred of the present invention are those listed below:



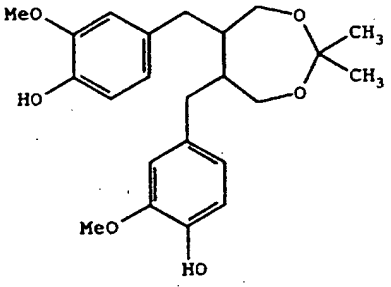
(IIa)



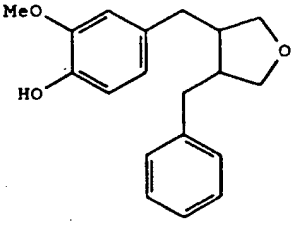
(IIb)



(IIIb)



(III'a)



(IVc)

The preferred pharmaceutical compositions of the invention, may contain any one or more of the preferred compounds as described above. Particularly preferred are those which contain one or more of the compounds (IIa), (IIb), (IIIa), (III'a) and (IVc). The compositions may contain any of the

pharmaceutically acceptable carriers normal in the art and are thus not particularly limited in this respect.

Any of the compounds (I) producible by the process of the present invention may be used to manufacture medicaments which are effective as SHBG inhibiting agents, anti-tumour agents, agents against prostate cancer and agents against benign prostatic hyperplasia. Particularly preferred compounds include all those mentioned above in regard to the preferred processes and products of the invention.

Preferred administration forms of the medicaments include tablet forms, i.v. injectable forms and suppositories.

Synthesis: Example 1, (±)-anhydrosecoisolariciresinol, (IVa) (see also Scheme 1)

Production of compound of type (Ia):

7.6 g (50 mmol) Vanillin (4-hydroxy-3-methoxybenzaldehyde) were dissolved in dried methanol with 7.3 g (50 mmol) succinic acid. 1 g (140 mmol) lithium was added to the solution. The lithium dissolved with evolution of hydrogen and heat and an orange colour developed. After 1.5 hours a further 1.1 g (157 mmol) lithium was added and the mixture was heated under reflux. After two days the resulting yellow precipitate was filtered off, dissolved in water, brought to pH 3 with 32 % hydrochloric acid and extracted with acetic acid. The organic phase was dried with sodium sulphate and placed under a vacuum. Final drying was carried out overnight under high vacuum. 13.3 g of a light yellow powder (a half ester) was obtained (82 % yield).

9.32 g (35 mmol) of the half-ester were dissolved in 200 ml dried methanol. After addition of 0.2 ml 96 % sulphuric acid the mixture was heated to reflux over two days. To the cooling solution one spatula (ca. 1 g) sodium

hydrogencarbonate was added and it was allowed to cool. The solvent was removed under vacuum and the solids were separated with water and acetic acid. the organic phase was dried over sodium sulphate. After recrystallisation from diethylether 7.85 g (28 mmol) of a white powder (a diester) were obtained (80 % yield).

Step (1) (production of compound of type (Ib)):
6.19 g (22 mmol) of the diester and 3.35 g (22 mmol) Vanillin were dissolved in 200 ml dried methanol. Then 1.5 g (0.21 mmol) lithium was added. After the reaction tapered off (1.5 h, red colouring) a further 6 g lithium was added in portions over 5 h and the mixture was heated under reflux over 2 days, producing a yellow precipitate. The solvent was removed and the precipitate taken up in 200 ml water. The aqueous red-brown solution was washed with 150 ml methylene chloride and subsequently neutralised with hydrochloric acid. In the aqueous phase a pH of 8 was set up with sodium hydrogencarbonate and extraction was carried out using methylene chloride. After acidification of the aqueous phase with hydrochloric acid (pH 2-3), the half ester was obtained as a yellow precipitate. The crystalline product was dried overnight under high-vacuum and 6.23 g (16 mmol) yellow powder was obtained (77 % yield).

Step (3) (steps (2) and (3) being reversible):
5.12 g (12.8 mmol) of the half-ester were dissolved in 150 ml dried methanol and 0.1 ml sulphuric acid were added. The reaction deposits were heated under reflux for two days. After addition of a spatula of sodium hydrogencarbonate, the solvent was removed and the solids separated with water and diethylether. The organic phase was dried over sodium sulphate and the solvent removed. A yellow-brown raw product was obtained. This could be purified through

recrystallisation from toluene giving 4.62 g (11 mmol) of the diester (85 % yield).

Step (2) (production of compound of type (II)):
2.02 g (4.8 mmol) of the diester were stirred in methanol with 200 mg Pd/C (5 % Aldrich) for 1 day under 2 atmospheres pressure of hydrogen. 1.79 g (4.3 mmol) of the saturated diester were obtained (89 % yield).

Step (4) (production of compound of formula (III)):
0.35 g (0.84 mmol) lithium aluminiumhydride were suspended in 50 ml dried THF. The suspension was cooled to -20 °C and 1 g (2.3 mmol)of the saturated diester in 50 ml THF was slowly added over 15 mins. The reaction mixture was brought to room temperature within two hours and stirred for a further two hours. After renewed cooling to 0 °C, 20 ml ethyl acetate were added and the mixture was stirred for 30 mins. and finally hydrolysed with 50 ml 2M hydrochloric acid. The THF was removed in a rotary evaporator, the aqueous phase extracted twice with 50 ml ethyl acetate and the purified organic phase was washed with saturated NaCl solution. 0.26 g (0.72 mmol) of the diol were obtained (86 % yield).

Step (5) (production of compound of type (IV):
100 mg (0.27 mmol) of the diol were dissolved in 20 ml acetone and heated under reflux for 20 mins. with 0.1 ml 60 % perchloric acid. One spatula of sodium hydrogencarbonate was added to the solution after cooling. After dilution with 50 ml diethylether, the solution was shaken twice with 50 ml sodium hydrogencarbonate solution and once with NaCl solution. The organic phase was dried over sodium sulphate and recrystallised from methanol. 0.08 g (0.23 mmol) of the final product, (±)-anhydrosecoisolariciresinol were obtained (87 % yield).

The total yield for the whole process was determined as approximately 29 %.

Characterisation NMR data: Example 1.1

For compound (IVa) and a selection of other compounds produced by the process of the present invention, NMR data are presented below.

Compound (IVa):

(500 MHz)

^1H: 2.15 m 2H $w_{h/2}$=15Hz; 2.50 dd 2H J=13.7 J´=7.9; 2.56 dd 2H J=13.7 J´=6.6; 3.52 dd 2H J=8.0 J´=5; 3.83 s 6H OMe; 3.93 dd 2H J=8.0 J´=6; 6.50 d 2H J=2; 6.57 dd 2H J=8 J´=2; 6.80 d 2H J=8

^{13}C: 59.30; 46.44; 73.26; 111.03; 111.07; 121.30; 132.30; 143.66; 146.30

Compound (±)-trans-(IIb):

(500MHz)

^1H: 2.85-3.05 m 6H; 3.60 s 3H; 3.62 s 3H; 3.79 s 3H; 5.5 s 1H 6.5 d; 6.58 dd 1H; 6.80 d 1H; 7.07 d; 7.2 m; 7.25 m;

^{13}C: 36.6; 36.9; 37.7; 38.0; 49.1; 49.5; 51.3; 51.66; 53.0; 53.1; 53.2; 57.2; 57.3; 112.7; 115.6; 115.7; 123.0; 123.1; 127.9; 128.0; 129.8; 129.8; 130.2; 130.4; 131.5; 131.7; 139.7; 145.6; 145.7; 147.8; 175.2; 175.3

Compound (±)-cis-(IIb):

(500MHz)

^1H: 2.69-2.91 m 4H; 3.2 m 2H; 3.52 s 3H; 3.53 s 3H; 3.83 s 3H; 5.48 s 1H; 6.59 m 2H; 6.78 d 1H J=8.4Hz; 7.11 2H; 7.18 m 1H; 7.24 m 2H

^{13}C: As for trans (±)-(IIb)

Compound (±)-trans-(IIIb):
(500MHz)

^{1}H: 1.86 m br 1H; 1.91 m br 1H; 2.54-2.9 m 6H; 3.52 m 2H; 3.82 m 5H; 6.60 d 1H J=1.8 Hz; 6.62 dd 1H J=1.8 Hz J'=7.9 Hz; 6.80 d 1H J=7.9 Hz; 7.16 m 3H; 7.26 m 2H

^{13}C: 35.85; 36.18; 43.98; 44.13; 55.86; 60.69; 111.37; 114.17; 121.64;126.01; 128.39; 129.05; 132.40; 140.62; 143.82; 146.43

Compound (±)-cis-(IIIb):
(500MHz)

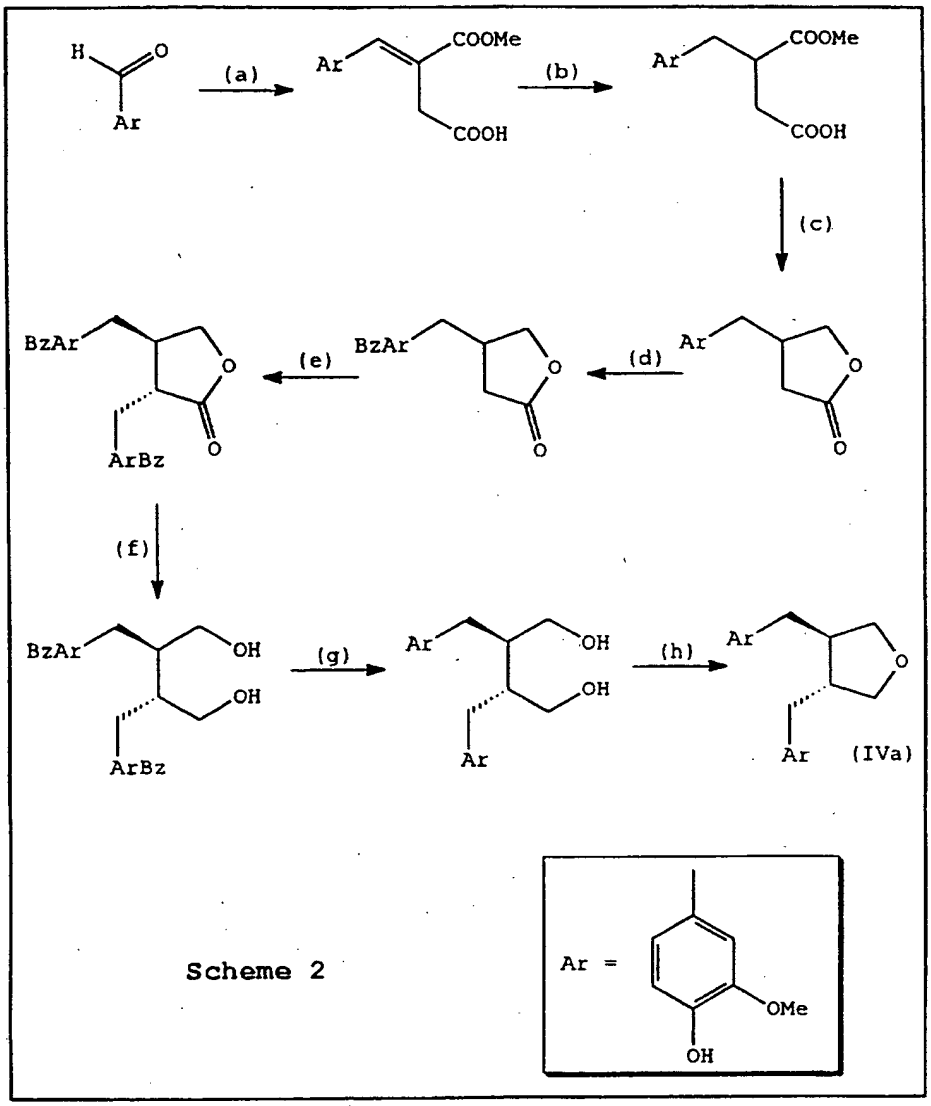
^{1}H: 1.98 m 1H; 2.08 m 1H; 2.62 m 3H; 2.72 dd 1H; 3.51 m 2H

^{13}C: As for trans (±)-(IIIb)

Comparative Synthesis: Example 2
(see also Scheme 2)

The known synthesis from the prior art (according to Brown and Daughan, *Heterocycles*, vol. 26, p. 1169, 1987) which most closely approaches the present synthetic route was carried out for compound (IVa) in order to indicate the improved yield associated with the present process.

Step (a):
A Stobbe condensation was carried out using vanillin and dimethyl succinate in a 1:1 equivalent ratio. 2.6 equivalents of lithium methoxide were added as base, without protecting the aryl hydroxyl groups. The ethylenic half-ester was obtained in 90 % yield.



Scheme 2

Step (b):

A catalytic hydrogenation of the half-ester was carried out using hydrogen and a palladium/carbon catalyst in the presence of acetic acid. The racemic half-ester was produced in 85 % yield. A separation of the enantiomers was not carried out at this stage, unlike in the prior art process, in order that the yield could be more realistically compared

with that of the present process, in which an enantiomer-separation step is not included.

Step (c):
The potassium salt of the racemate was reduced in ethanol using a tenfold excess of $Ca(BH_4)_2$ producing the corresponding butyrolactone derivative in 83 % yield.

Step (d):
The hydroxyl group of the aromatic ring was transformed into a benzoxy group by reaction with benzyl chloride in chloroform. The product was obtained in 90 % yield.

Step (e):
The lithium anion of the protected lactone was formed using LHDS in THF at -80°C and was reacted with 1 equivalent of 4-benzoxy-3-methoxy-benzylbromide. The product was purified using chromatography and a yield of trans-dialkylated product of 87 % was obtained.

Step (f):
The lactone ring of the trans-dialkylated product was then reduced using $LiAlH_4$ in THF at room temperature to give the corresponding diol in 66 % yield.

Step (g):
A catalytic hydrogenation of the diol using palladium/carbon in ethyl acetate resulted in an 76 % yield of (±)-secoisolarici-resinol.

Step (h):
The resulting diol was dehydrated by means of $HClO_4$ to form the related cyclic ether compound, (±)-

anhydrosecoisolariciresinol, (IVa), in 74 % yield, after chromatographic purification.

The total yield for the process was determined as 18 %. Thus this comparative example indicates that the process of the present invention shows a 61 % increase in the available yield in comparison to the closest prior art process, and can be carried out under less stringent conditions in a lesser number of steps.

Concentration Dependence: Example 3

In order to determine the strength of the interaction of the compounds produced according to the present invention, tests were carried out investigating remaining SHBG activity to 5α-dihydrotestosterone (DHT) with varying concentrations of the compounds, DHT being a natural hormone that binds with SHBG.

The results for compound (IVa) are depicted in Figure 1. Figure 1 is a graph of the remaining activity of SHBG against the concentration of (IVa). Two different plots appear on the graph, the lower one corresponding to a DHT concentration of 4.6 nM and the upper to a DHT concentration of 9.2 nM. From the latter plot it can be determined that a remaining SHBG activity of 50 % is seen at a concentration of around $1.4*10^{-6}$ M. This compound is therefore the most active, when compared with other preferred compounds (see Table 1). Clearly, as the concentration of (IVa) increases, so the remaining activity of SHBG decreases. As the concentration of DHT is increased, more (IVa) is required to reduce the activity of SHBG by the same amount.

The results of further tests on other preferred compounds are indicated in Table 1. In these experiments a DHT

concentration of 9.6 nM was used. From the results it can be seen that compounds (IV) and (V) are particularly effective. Additionally, it is also clear that compounds which possess one MeO and one OH group on the aromatic rings are also very effective.

Compound	Remaining SHBG Activity
IIa	30 % @ $6*10^{-4}$M
IIIa	50 % @ $3.2*10^{-4}$M
Va	50 % @ $8.3*10^{-5}$M
IVd	33 % @ $7*10^{-5}$M
IVb	53 % @ $6.7*10^{-5}$M
Vd	50 % @ $6.9*10^{-5}$M
Vb	82 % @ $6.5*10^{-5}$M
Vf	50 % @ $1.4*10^{-3}$M
Vc	81 % @ $8.4*10^{-4}$M
IIc	61 % @ $7.8*10^{-4}$M
III'a	75 % @ $6.2*10^{-4}$M
IIb (±)-trans	35 % @ $1.3*10^{-4}$M
IIb (±)-cis	95 % @ $1.3*10^{-4}$M
IIIb (±)-trans	36 % @ $1.6*10^{-5}$M
IIIb (±)-cis	75 % @ $1.6*10^{-5}$M

Table 1

Method of inhibition: Example 4

In order to be able to estimate the association constants of the compounds, it must be determined whether they compete with DHT for the protein, or whether three-species complexes of the type compound-protein-DHT can form. This can be decided using a graph-analogue according to Lineweaver-Burk (Rousseau *et al*, *Nature*, vol. 284, p. 485, 1980).

The specific SHBG activity was thus determined at five differing ^{3}H-DHT concentrations, each at (IVa) concentrations

of 0 M, $2.9*10^{-5}$ M and $5.8*10^{-5}$ M. The total binding activity and the unspecific binding activity (USB) were also measured. The results are outlined in Table 2.

^{3}H DHT /nM	Total activity /cpm	USB /cpm	Activity at 0 M IVa	Activity at $2.9*10^{-5}$ M IVa	Activity at $5.8*10^{-5}$ M IVa
46.0	19119	938	3223	1752	1446
18.4	16425	747	2270	1231	1088
13.8	13080	590	2075	1047	836
9.2	8016	433	1786	677	518
4.6	4141	227	928	288	287

Table 2

The linear regression in a plot of 1/free DHT against 1/bound DHT results in an intersect with the Y-axis and thereby indicates that a competitive "inhibition" of the protein by (IVa) occurs. This graph is depicted in Figure 2.

Estimation of equilibrium constants K_a: Example 5

With the assumption of competitive binding the estimation of equilibrium constants is possible. Two reactions exist in competition with one another:

$$P + S \overset{K_{a1}}{\rightleftharpoons} PS$$

$$P + I \overset{K_{a2}}{\rightleftharpoons} PI$$

At a concentration of the inhibitor, (I), at which the concentration of the protein-substrate complex (PS) has reduced by half, the protein-substrate complex concentration becomes equal to the protein-inhibitor concentration, (PI). This is the basis for the formula:

$$K_{a2} = \frac{K_{a1}}{\frac{1}{RBA}(1+R)-R}$$

K_{a1} = association constant DHT/SHBG
K_{a2} = association constant inhibitor/SHBG
R = spec. bound/free DHT at 50% inhibition
RBA = relative binding activity = DHT_{total}/$inhibitor_{total}$ at 50% inhibition

50 % inhibition is reached at a concentration of (IVa) of $1.4*10^{-6}$ M, at a DHT concentration of $9.2*10^{-9}$ M. An association constant of ca. $4*10^{6}$ M^{-1} thereby results.

The association constants for some of the other important compounds are listed in Table 3.

Compound	K_a (M^{-1})
IIa	$6.0*10^4$
IIIa	$2.0*10^4$
Va	$7.7*10^4$
IVd	$3.0*10^5$
IVb	$1.0*10^5$
Vd	$9.3*10^4$
Vb	$0.5*10^4$
Vf	$0.5*10^4$

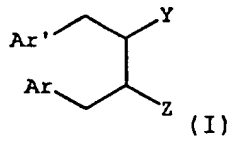
Table 3

These results confirm the nature of the data already presented in Table 1.

From the examples in general it can be seen that the compounds producible by the process of the present invention exhibit very favourable binding properties with SHBG, thus having important pharmacological properties.

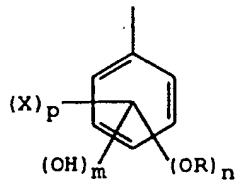
Claims:

1. A process for the production of compounds of formula (I):

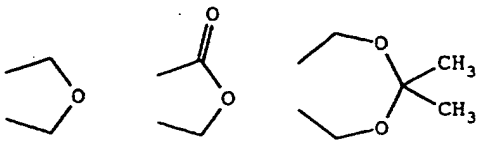


(I)

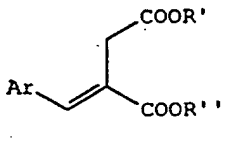
wherein Ar and Ar' may be the same or different and are represented by groups of the following formula:



wherein X is a halogen atom, a C_1 to C_6 alkyl group, an amino group, a nitro group, an acyl group (CH_3COO-), a carboxylic acid group or a C_1 to C_6 alkyl ester of a carboxylic acid, a phenyl group, or a phenyl group substituted with any of the above groups; R is a C_1 to C_6 alkyl group; and n, m and p are integers of 0 to 5, provided that the sum of n, m and p does not exceed 5; and Y and Z may be the same or different and represent COOH, COOR', CH_2OH, or CH_2OR' groups or taken together may represent any groups of the following formulae:

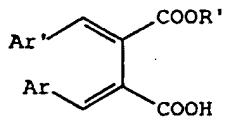


comprising step (1), of reacting a compound of formula (Ia):



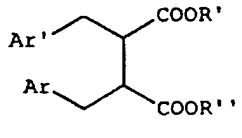
(Ia)

with a lithium/R'OH, or a lithium/R''OH mixture in the presence of Ar'-CHO, wherein R' and R'' may be the same or different and are C_1 to C_6 alkyl groups, or phenyl groups to form an intermediate compound (Ib):



(Ib)

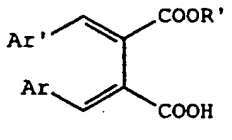
2. The process according to claim 1 for the production of compounds of formula (II):



(II)

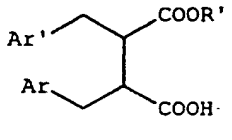
comprising the process step of claim 1, and the additional following steps:

(2) Reducing compounds of formula (Ib),



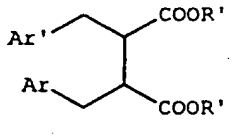
(Ib)

to produce compounds of formula (Ic);



(Ic)

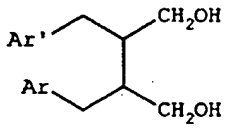
(3) Subjecting compounds (Ic) to esterification, to produce compounds of formula (II);



(II)

wherein Ar, Ar', R' and R'' have the same meanings as defined in claim 1, and wherein reduction step (2) is preferably carried out using hydrogen and a palladium/carbon catalyst, and the esterification step (3) is preferably carried out using R''OH and sulphuric acid.

3. The process according to claim 2 for the production of compounds of formula (III):

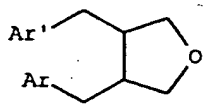


(III)

comprising the additional step (4) of reducing compounds (II) to form compounds (III);

wherein Ar and Ar' have the same meanings as defined in claim 1, and wherein reduction step (4) is preferably carried out using $LiAlH_4$.

4. The process according to claim 3 for the production of compounds of formula (IV):

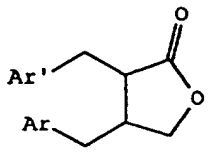


(IV)

comprising the additional step (5) of subjecting compounds of formula (III) to a cyclisation reaction, to produce compounds of formula (IV);

wherein Ar and Ar' have the same meanings as defined in claim 1 and wherein cyclisation step (5) is preferably carried out using $HClO_4$.

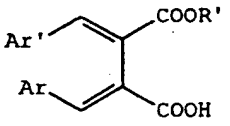
5. The process according to claim 4 for the production of compounds of formula (V):



(V)

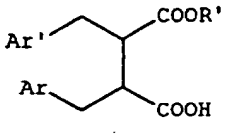
comprising the process step according to claim 1, and the additional following steps:

(2) Reducing compounds of formula (Ib),



(Ib)

to produce compounds of formula (Ic);



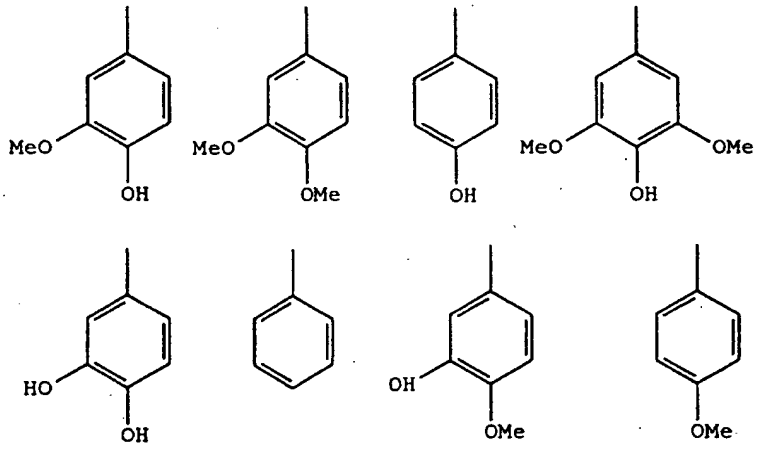
(Ic)

(6) Subjecting compounds of formula (Ic) to a cyclisation reaction to form compounds of formula (V);

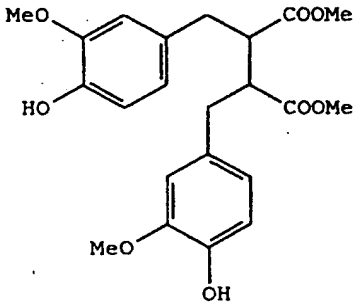
wherein Ar, Ar' and R' have the same meanings as defined in claim 1 and wherein the reduction step (2) is preferably carried out using hydrogen and a palladium/carbon catalyst, and the cyclisation step (6) is preferably carried out using $LiAlH_4$ followed by hydrochloric acid.

6. The process according to any one of the preceding claims wherein R' and R'' are each methyl groups.

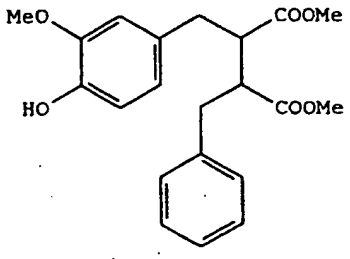
7. The process according to any one of the preceding claims wherein Ar and Ar' are independently selected from the following groups:



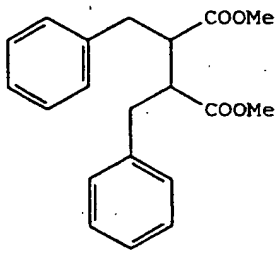
8. The process according to claim 2 wherein the following compounds are produced:



(IIa)

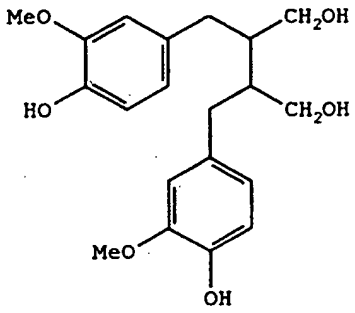


(IIb)

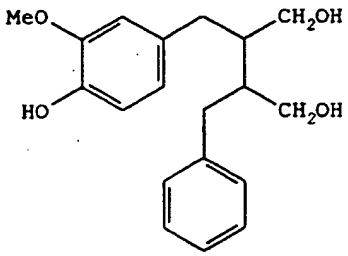


(IIc)

9. The process according to claim 3 wherein the following compounds are produced:

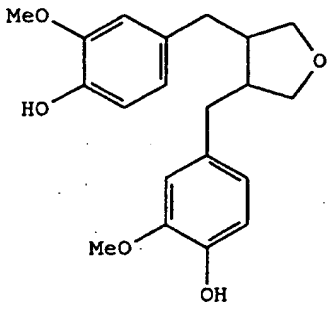


(IIIa)

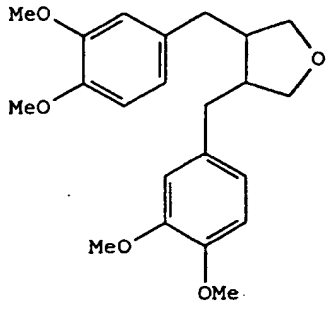


(IIIb)

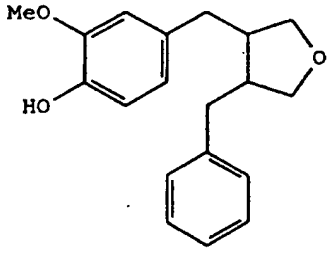
10. The process according to claim 4 wherein the following compounds are produced:



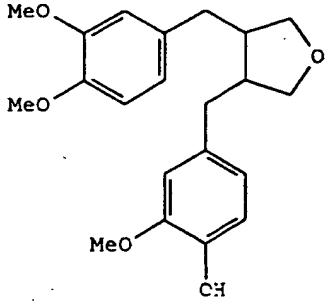
(IVa)



(IVb)

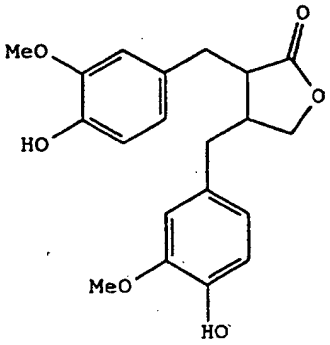


(IVc)

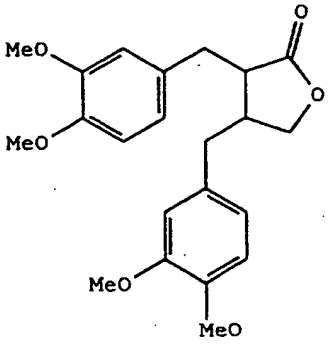


(IVd)

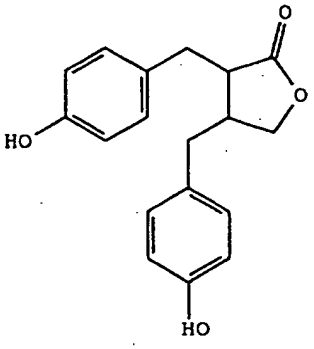
11. The process according to claim 5 wherein the following compounds are produced:



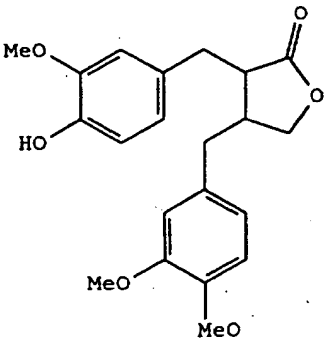
(Va)



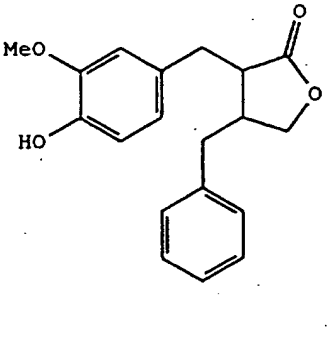
(Vb)



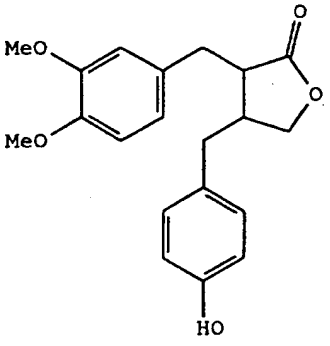
(Vc)



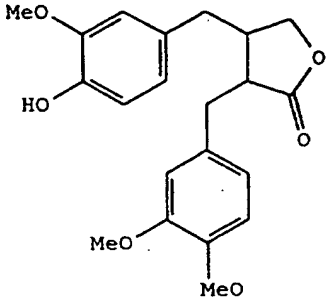
(Vd)



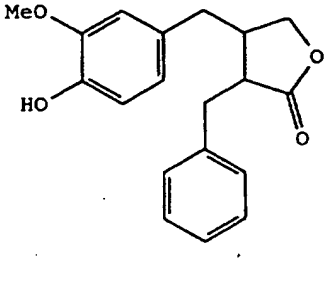
(Ve)



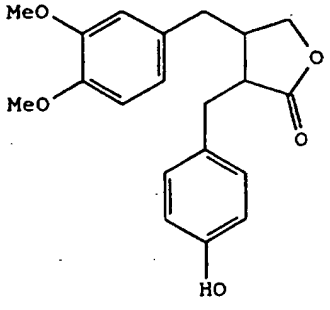
(Vf)



(Vg)

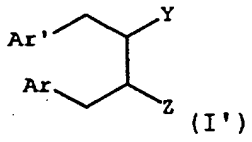


(Vh)

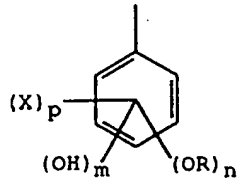


(Vj)

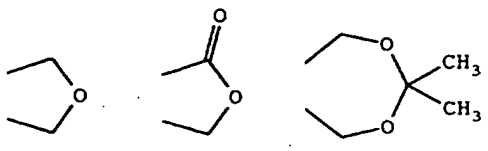
12. A compound of the general formula (I'):



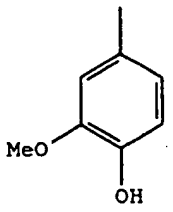
wherein Ar and Ar' may be the same or different and are represented by groups of the following formula:



wherein X is a halogen atom, a C_1 to C_6 alkyl group, an amino group, a nitro group, an acyl group (CH_3COO-), a carboxylic acid group or a C_1 to C_6 alkyl ester of a carboxylic acid, a phenyl group, or a phenyl group substituted with any of the above groups; R is a C_1 to C_6 alkyl group; and n, m and p are integers of 0 to 5, provided that the sum of n, m and p does not exceed 5; and Y and Z may be the same or different and represent COOH, COOR', CH_2OH, or CH_2OR' groups or taken together may represent any groups of the following formulae:

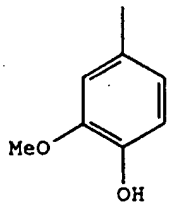


wherein, compounds having p = 0, (m + n) = 3 or less and R = Me are not claimed, except where Ar' is a group of formula:

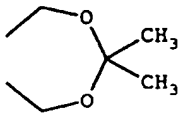


and either:

Ar is a group of the following formula:

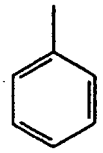


and Y and Z are both COOR' groups, or together form group of formula



or:

Ar is a group of formula:

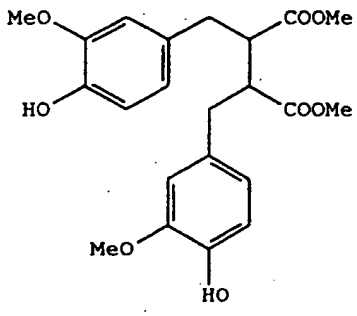


and Y and Z are both COOR' groups, or both a CH_2OH group, or together form a group of formula:

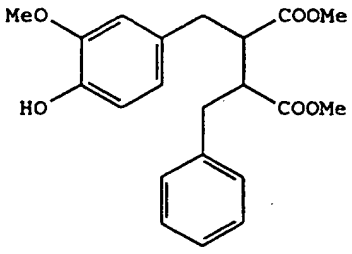
wherein when Y and Z are COOR', the groups R' may be the same or different and are C_1 to C_6 alkyl groups or phenyl groups.

13. Compounds according to claim 12 wherein p = 0, (m + n) = 3 or less and R = Me, in which if Y and/or Z are COOR' groups, R' is a C_1 to C_6 alkyl group, and when both Y and Z are COOR' groups, they are the same.

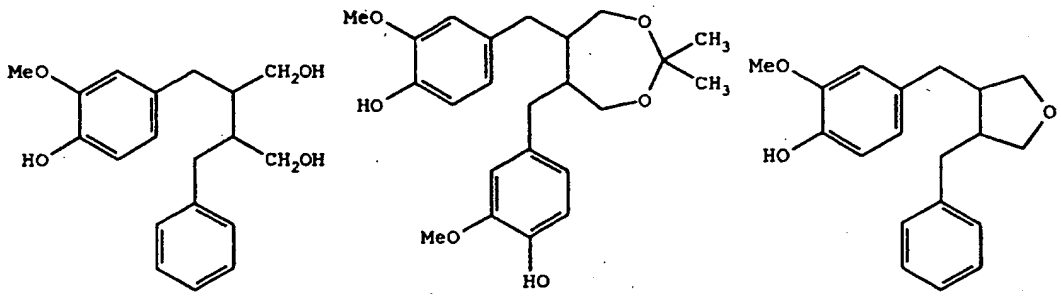
14. The compounds according to claims 12 or 13 having the following formulae:



(IIa)



(IIb)



(IIIa) (III'a) (IVc)

15. The use of one or more compounds of formula (I) as defined in claim 1 in the manufacture of a medicament effective as a human sex hormone-binding globuline inhibitor, or as an anti-tumour agent or as a medicament effective against prostate cancer, or as a medicament effective against benign prostatic hyperplasia.

16. The use according to claim 15, wherein the compounds are those of formula (II) as defined in claim 2, those of formula (III) as defined in claim 3, those of formula (IV) as defined in claim 4 or those of formula (V) as defined in claim 5.

17. The use according to claim 16 wherein the compounds are selected from any one or more of (IIa), (IIb) and (IIc) as defined in claim 8, from any one or more of (IIIa) and (IIIb) as defined in claim 9, from any one or more of (IVa), (IVb) (IVc) and (IVd) as defined in claim 10 or from any one or more of (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg) and (Vj) as defined in claim 11.

18. The use according to claim 17 when the compound is anhydrosecoisolariciresinol, (IVa).

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds selected from those of the general formula (I') as defined in claim 12 and/or from compound (IVa).

20. A pharmaceutical composition according to claim 19, wherein the compounds are selected from those as defined in claims 13 or 14.

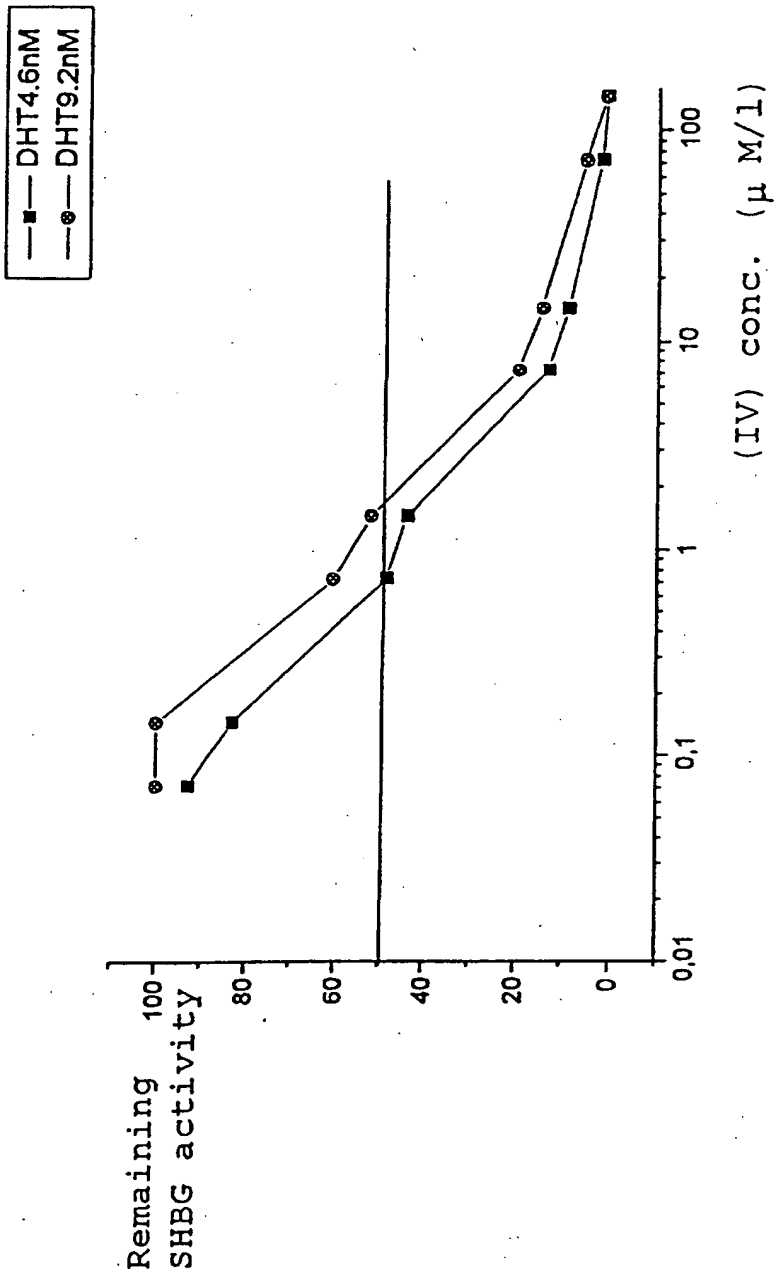

DHT4.6nM
DHT9.2nM
Remaining SHBG activity
100
80
60
40
20
0
0,01
0,1
1
10
100
(IV) conc. (μ M/l)

Figure 1

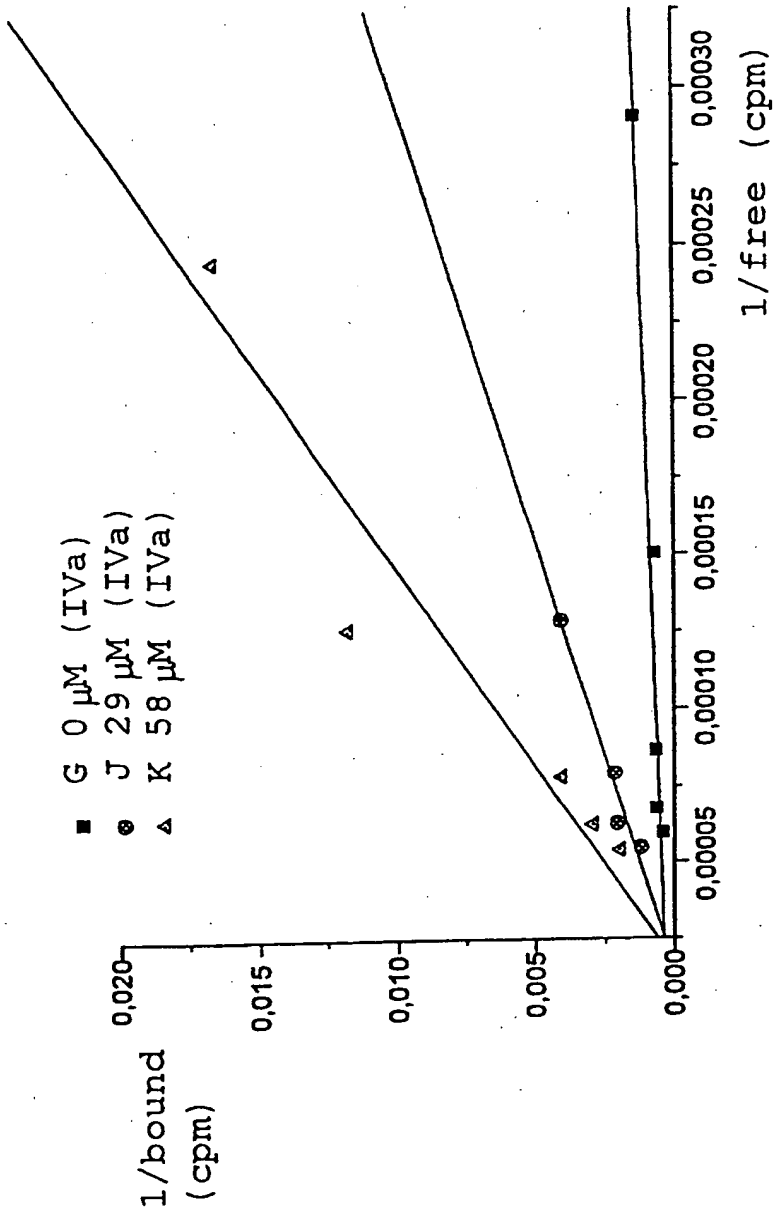

G 0 µM (IVa)
J 29 µM (IVa)
K 58 µM (IVa)
1/bound (cpm)
0,020
0,015
0,010
0,005
0,000
0,00005
0,00010
0,00015
0,00020
0,00025
0,00030
1/free (cpm)

Figure 2

INTERNATIONAL SEARCH REPORT

Inter. al Application No
PCT/EP 95/04096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C69/734 C07C67/343 C07C67/08 C07C67/303 C07C33/26
C07C29/147 C07D307/12 C07C43/23 C07D313/04 A61K31/34
A61K31/225 A61K31/05 A61K31/085 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 14, no. 197 (C-0712), 23 April 1990 & JP,A,02 040323 (TSUMURA & CO), 9 February 1990, see abstract ---	1-18
Y	PATENT ABSTRACTS OF JAPAN vol. 13, no. 553 (C-663), 8 December 1989 & JP,A,01 228928 (TSUMURA & CO), 12 September 1989, see abstract -----	1-18

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1996	20. 06. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kinzinger, J